## REMARKS

Reconsideration of this application, as amended, is respectfully requested. Claims 1-31 are pending.

## I. Species Election Requirement

In response to the species election requirement, applicants elect the species 5-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid. The elected species is recited in claim 27, lines 3 and 4.

## II. Amendments

Claims 1, 3-8 and 28 are also amended to correct clerical errors.

Claim 1 is amended to correct the spacing in the term "interacts with" in paragraph IV, and to correct an obvious misspelling of "site" at paragraph VI.

Claim 3 is amended to correct the spacing in the term "features VI through XXXVII" in paragraph V.

Claim 4 is amended to correct an obvious misspelling of "from" in the first line.

Claim 5 is amended to correct the distance recited in paragraph IV. Support for this amendment is found in the application as filed, for example at page 27, lines 5-8.

Claim 6 is amended to correct the punctuation at line 2.

Claims 7 and 8 are amended to correct the spacing in the term "a carboxylic acid" at paragraph II.

Claim 28 is amended to correct the spacing of the term "claim 1."

Claims 1, 3, 5 and 6 are also amended to add a period at the end of the claim.

The amendments to claims 29 and 30 address the Examiner's concerns expressed during a telephone conference of November 12, 2002.

Claim 29 is amended at the request of the Examiner to delete the phrase "including a human." New claim 31 recites the method of claim 29 wherein the mammal is a human.

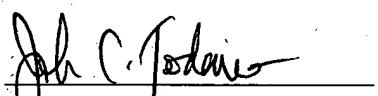
Claim 30 is amended at the request of the Examiner to delete "various forms of cancer and malignant diseases," and instead recite "cancers." This is not a narrowing amendment. The term "cancers" covers all diseases characterized by malignant neoplasm. See, *e.g.*, *Stedman's Medical Dictionary*, p. 268 (1995) (Exhibit A) ("Cancer" defined as "any of various types of malignant neoplasms, most of which invade surrounding tissues, may metastasize to several sites, and are likely to

recur after attempted removal and to cause death of the patient unless adequately treated.").

## III. Conclusion

All claims 1-31 are believed to be in condition for allowance. Favorable action is earnestly solicited.

Respectfully submitted,



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Docket No: 0776/1H462US1

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PATENT TRADEMARK OFFICE

Customer No.:

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Henrik Sune ANDERSEN et al.

Serial No.: 09/659,622 Art Unit: 1614

Confirmation No.: 5060

Filed: September 11, 2000 Examiner: Frederick F. Krass

For: METHOD OF INHIBITING PROTEIN TYROSINE PHOSPHATASE 1B AND/OR 5-CELL PROTEIN TYROSINE PHOSPHATASE AND/OR OTHER PTPASES WITH AN ASP RESIDUE AT POSITION 48

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**MARKUP TO PRELIMINARY AMENDMENT**

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

January 27, 2003

Sir:

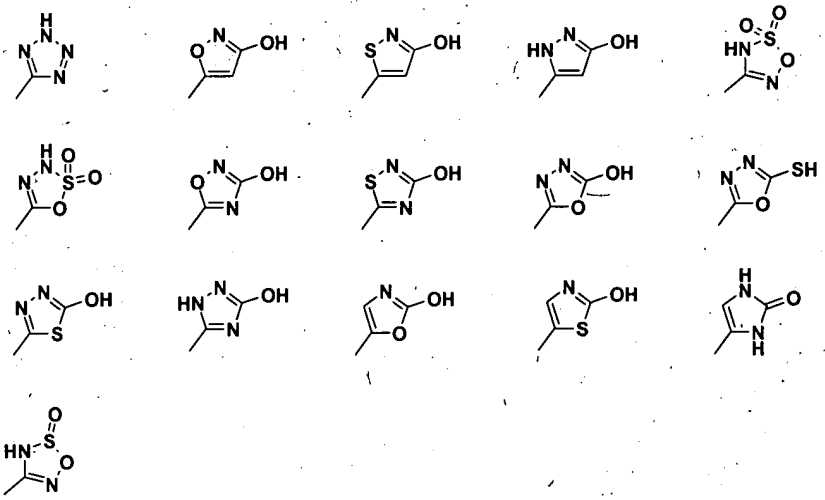
Pursuant to 37 C.F.R. §1.121(c)(1)(ii), please amend claims 1, 3-8 and 29-30 as follows.

**IN THE CLAIMS**

1. (Amended) A method of inhibiting at least one intracellular or membrane-associated PTPase that has aspartic acid (Asp) in position 48 using the numbering for PTP1B, the method comprising exposing the PTPase to an inhibitor compound which fits spatially into the active site and the vicinity thereof, said compound comprising the following features and moieties:

   I. a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and a hydrogen bond with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; and

   II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles



   wherein said acid or said isostere group forms a salt bridge to the side chain amino group of lysine 120 wherein the distance between the centroid of said carboxylic acid or carboxylic acid isostere and

the side chain nitrogen atom of said Lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å;

and at least one of features IV through V:

IV. a hydrophobic group that [interactswith] interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; and

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and

one or more of the following features VI-XXXVII:

VI. an amino group which forms a salt bridge to the [site] side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of said [site] side chain carboxylic acid group of aspartic acid 48 ranges from 3.4-4.1 Å; and

VII. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å

and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å; and

VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;

IX. a hydrophilic group that forms a hydrogen bond or forms a salt bridge with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;

X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 is 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;

XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;

XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 is 2 ranges from.7-4.0 Å;

XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48

such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;

XIV. a hydrophilic group that interacts with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;

XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVII. a hydrophobic group that reaches a proximity interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;

XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

XXVI.a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

XXVII.a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXVIII.a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXIX.a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

XXX. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXI.a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of

said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXII.a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XXXIII.a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

XXXIV.a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

XXXV.a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

XXXVI.a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

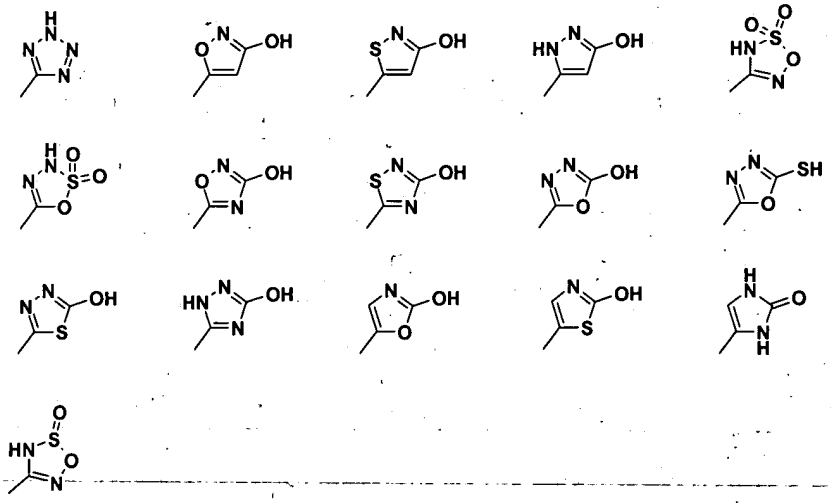
XXXVII.a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and (i) the centroid of the side chain of said methionine 258 ranges from 4.1-7.2 Å, (ii) the centroid of said glycine 259 ranges from 4.7-7.7

Å, and (iii) the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å[;].

3. (Amended) A method of inhibiting at least one PTPase selected from the group consisting of PTP1B, TC-PTP and other PTPase that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity therof , said compound comprising the following features and moieties:

I. a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles



wherein said acid or acid isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and one or more of the following features IV and V:

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; and/or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and

one or more of the following [featuresVI] <u>features VI</u> through XXXVII:

VI. an amino group which forms a salt bridge to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of

said side chain carboxylic acid group of aspartic acid 48 ranges from 3.4-4.1 Å; and

VII. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å; and

VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;

IX. a hydrophilic group that forms a salt bridge with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;

X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;

XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;

XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 ranges from 2.7-4.0 Å;

XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;

XIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;

XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic

group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVII. a hydrophobic group that interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;

XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of

said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic

group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXVIII. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXIX. a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

XXX. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXII.a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XXXIII.a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

XXXIV.a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

XXXV.a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

XXXVI.a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

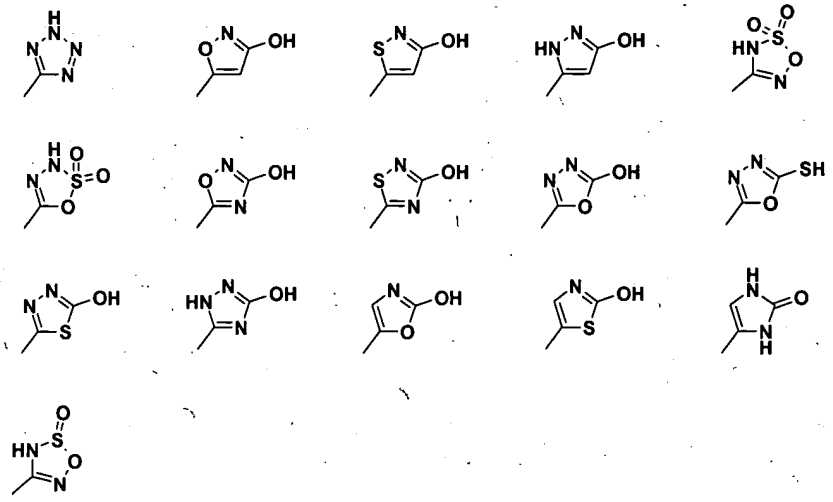
XXXVII.a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges

from 4.1-7.2 Å, the centroid of said glycine 259 ranges from 4.7-7.7 Å, and the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å[;].

4. (Amended) A method of inhibiting at least one PTPase selected [form] from the group consisting of PTP1B, TC-PTP and other PTPase that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising the following features and moieties:

I. an oxalylamide which forms a salt bridge to the guanidinium group of arginine 221 and forms a hydrogen bond with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalylamide group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalylamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) carboxylic acid isostere group selected from the following 5-membered heterocycles



wherein said acid or said isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said Lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and

at least one of the following features IV and V:

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; and/or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic

group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and

at least one of the following features VI through XXXVII:

VI. an amino group which forms a salt bridge to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 3.4-4.1 Å; and

VII. two oxygen atoms which forms hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å; and

VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;

IX. a hydrophilic group that forms a hydrogen bond with aspartic acid 181 such that the distance between the centroid of said hydrophilic

group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;

X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;

XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;

XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 ranges from 2.7-4.0 Å;

XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;

XIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;

XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVII. a hydrophobic group that interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;

XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the

centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXVIII. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXIX. a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

XXX. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXII. a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XXXIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

XXXIV. a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

XXXV.a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

XXXVI.a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

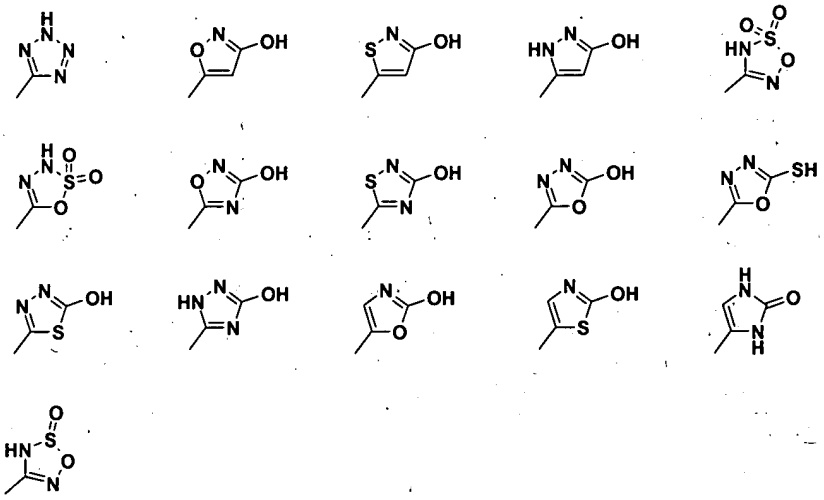
XXXVII.a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.1-7.2 Å, the centroid of said glycine 259 ranges from 4.7-7.7 Å, and the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å;

5. (Amended) A method of inhibiting a PTPase selected from the group consisting of PTP1B, TC-PTP and other PTPases that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising the following features and moieties:

I. a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate

isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles



wherein said acid or said isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said Lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and

at lest one of the following features IV and V:

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from [3.55.1] 4.4 - 5.1 Å; and/or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 is 4.4-6.5 Å; and one or more of the following features VI-XXXVII

VI. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å;

VII. an amino group which forms a salt bridge to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of said side chain carboxylic acid group of aspartic acid 48 is 3.4-4.1 Å;

VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;

IX. a hydrophilic group that forms a hydrogen bond with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;

X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;

XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;

XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 ranges from 2.7-4.0 Å;

XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic

group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;

XIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;

XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVII. a hydrophobic group that interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;

XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance

between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXVIII. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXIX. a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid

of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

XXX. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXII. a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XXXIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

XXXIV. a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said

hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

XXXV. a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

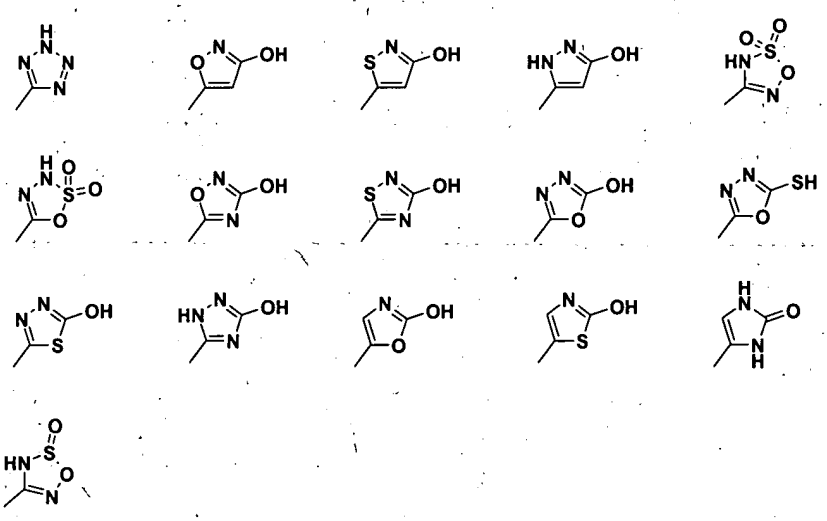
XXXVI. a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

XXXVII. a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.1-7.2 Å, the centroid of said glycine 259 is 4.7-7.7 Å, and the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å[;].

6. (Amended) A method of inhibiting a PTPase selected from the group consisting of PTP1B[.], TC-PTP and other PTPases that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising the following features and moieties:

I. an oxalylamide which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalylamide group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalylamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles



wherein said acid or said isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said Lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and at least one of the following features IV and V

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; and

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and at least one of the following features VI through XXXVII:

VI. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å; and

VII. an amino group which forms a salt bridge to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of

said side chain carboxylic acid group of aspartic acid 48 ranges from 3.4-4.1 Å;

VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;

IX. a hydrophilic group that forms a hydrogen bond with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;

X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;

XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;

XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47

such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 ranges from 2.7-4.0 Å;

XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;

XIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;

XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XVII. a hydrophobic group that interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of

said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;

XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXVIII.a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

XXIX.a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

XXX. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXI.a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXII.a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XXXIII.a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid-48 such that the

distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

XXXIV.a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

XXXV.a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

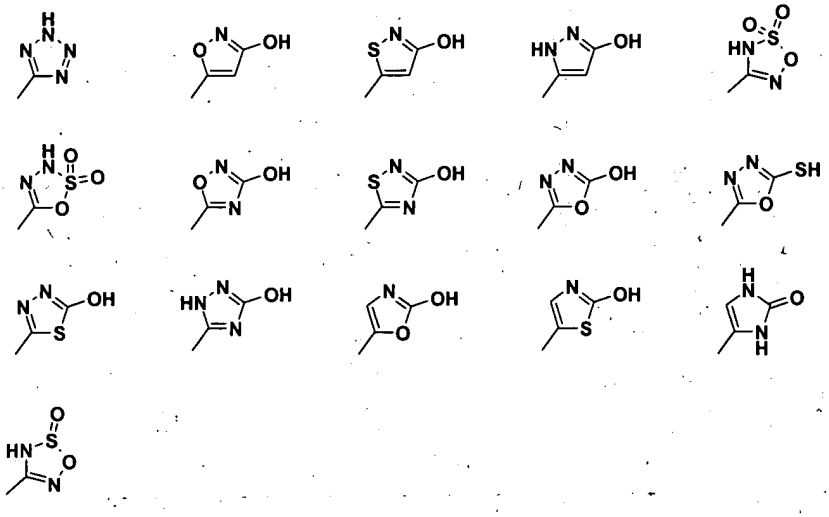
XXXVI.a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

XXXVII.a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.1-7.2 Å, the centroid of said glycine 259 ranges from 4.7-7.7 Å, and the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å[;].

7. (Amended) A method of inhibiting at least one PTPase selected from the group consisting of Protein Tyrosine Phosphatase 1B (PTP1B) and/or T-Cell Protein Tyrosine Phosphatase which (TC-PTP) and/or other PTPases that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising:

I. a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and forms a hydrogen bond with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) [acarboxylic] <u>a carboxylic</u> acid isostere group selected from the following 5-membered heterocycles



wherein said acid or isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and at least one of the following features IV and V:

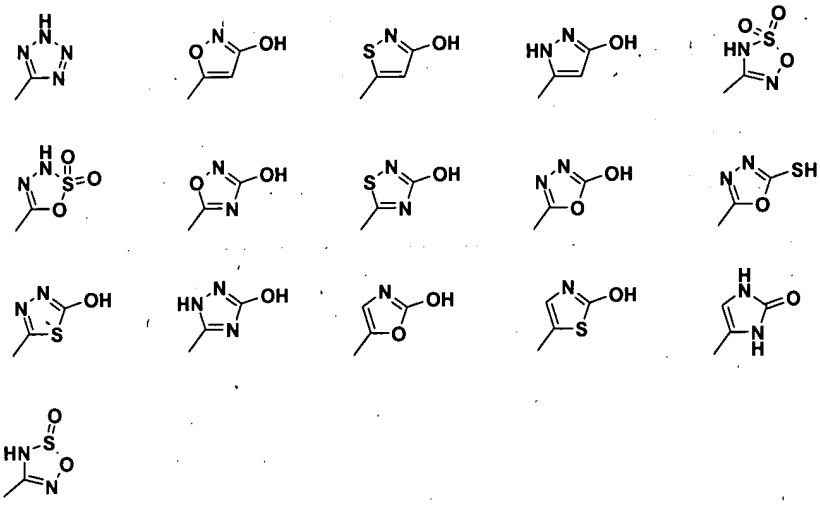
IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å.

8. (Amended) A method of inhibiting at least one PTPase selected from the group consisting of Protein Tyrosine Phosphatase 1B (PTP1B), T-Cell Protein Tyrosine Phosphatase and other PTPases that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity therof, said compound comprising:

I. an oxalylamide which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalylamide group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalylamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) [acarboxylic] <u>a carboxylic</u> acid isostere group selected from the following 5-membered heterocycles



wherein said acid or isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 wherein the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and at least one of the features IV and V:

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å.

28. (Amended) The method of [claim1] claim 1 wherein said compound is of the Formula 1.

29. (Amended) The method of any one of claims 1 to 10 wherein said exposing step is effected by administering said compound to a mammal [including a human] in need of said inhibition.

30. (Amended) The method of claim 29, wherein said mammal has a disease selected from the group consisting of autoimmune diseases, acute and chronic inflammation, osteoporosis, [various forms of cancer and malignant

diseases] <u>cancers</u>, [and] type I diabetes, type II diabetes, and obesity.

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